

A Dissertation on
**FACTORS INFLUENCING THE OUTCOME OF
THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION
AMONG NON SMOKERS**

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QUESTIONNAIRE

MASTER CHART

INTRODUCTION

Coronary Artery Disease is defined as “an impairment of heart function due to inadequate blood flow to the heart compared to its needs, caused by obstructive changes in the coronary circulation to the heart”.

It has been declared by WHO as a Modern epidemic.

It was the brilliant work of Herrick in 1912 who performed autopsy on AMI patients, that put forward the new concept of thrombotic occlusion of coronary artery as the cause of downstream necrosis of heart muscle.

The definitive proof for the above said concept came from angiographic studies performed during the early hours of acute coronary event.

This prompted scientists to systematically test the thrombolytic strategies to treat AMI, opening a new era of thrombolytic therapy in AMI.

Scientists have developed many effective thrombolytic drugs like streptokinase, tenecteplase, reteplase, urokinase, APSAC (Anisoylated plasminogen streptokinase activator complex) etc.

Evidence for the use of thrombolytic therapy came from large multicentric studies. GISSI and ISIS – 2 confirmed decrease in mortality with the early use of streptokinase. ISA (I.V.SK in acute MI study group) also stands as a proof of efficiency of thrombolytic drugs to decrease mortality.

Success rate of thrombolysis and thus the overall reduction of mortality is different among different agents used. The GUSTO-1 trial showed a 30 days mortality of 6.3% for accelerated t-pA versus 7.4% for SK with I.V. heparin.

But because of the prohibitive cost of tpA, SK became the sheet anchor for thrombolytic therapy in GRH. Thrombolytic treatment has revolutionised the management of AMI. GUSTO angiographic substudy showed a success rate of 54% at 90 mins using I.V. SK and heparin.

Thrombolytic treatment has been consistently proven to reduce the mortality and morbidity. In spite of this it has been recognized that thrombolytic treatment has failed in a significant population. There is a lot of room for improvement. We need to identify the factors that are responsible for failure of thrombolysis.

Smoking is a proven risk factor for acute MI. There have'nt been too many studies done to analyse the effect of various factors influencing outcome of thrombolysis among non smokers. Studies have been done predominantly to know the influence of smoking on the outcome thrombolysis.

With this back ground, we decided to look into our own patients (non smokers) who receive SK for Acute MI in the ICCU of GRH.

AIM OF STUDY

1. To find out the overall success rate of thrombolysis in ICCU of GRH among non smokers.
2. To find out whether the following parameters influence the outcome of thrombolysis among non smokers.
 - a. Age
 - b. Sex
 - c. Systemic Hypertension
 - d. Diabetes mellitus
 - e. Location of Myocardial infarction
 - f. Time interval between onset of pain and initiation of thrombolytic therapy.

REVIEW OF LITERATURE

CORONARY CIRCULATION

The coronary circulation is unique in that it is responsible for generating the arterial pressure that is required to perfuse the systemic circulation and yet, at the same time, has its own perfusion impeded during the systolic portion of the cardiac cycle. Because myocardial contraction is closely connected to coronary flow and oxygen delivery, the balance between the oxygen supply and demand is a critical determinant of the normal beat to beat function of the heart. When this relationship is acutely disrupted by diseases affecting the coronary blood flow, the resulting imbalance can immediately precipitate a vicious cycle, whereby ischemia induced contractile dysfunction precipitates hypotension and further myocardial ischemia. Thus a knowledge of the regulation of coronary blood flow, determinants of myocardial oxygen consumption, and the relationship between ischemia and contraction is essential.

In contrast to most other vascular beds, myocardial oxygen extraction is near maximal at rest, averaging approximately 75% of arterial oxygen content².

BLOOD SUPPLY TO THE HEART

The epicardial coronary artery system⁶¹ consists of the left and right coronary arteries, which normally arise from ostia, located in the left and right sinuses of valsalva, respectively. In about 50% of humans a “third coronary artery” (conus artery) arises from a separate ostium in the right sinus.

The left main (LM) coronary artery bifurcates into the left anterior descending (LAD) and left circumflex (LCX) branches⁶². The dominant right coronary artery (RCA) gives rise to

the posterior descending artery (PDA).

BRANCHES OF THE MAJOR EPICARDIAL ARTERIES

The branches of the LAD artery, in their usual order of origin, are the first diagonal, the first septal perforator, the right ventricular (not always seen in normal hearts), other septal perforators and other diagonal branches.

The branches of the LCX are variable but may include the sinus node artery (40 – 50%), the left atrial circumflex branch, one or more posterolateral marginals and the PDA (10 – 15%).

The branches of the RCA include the conus artery, the artery to the sinus node (50 – 60%), several anterior right ventricular branches, right atrial branches, the acute marginal branch, the artery to the AV node and proximal bundle branches, the PDA and terminal branches to the left ventricle and left atrium. In 40 – 50% of hearts the sinus node artery originates from the proximal LCX.

CORONARY ARTERY DISTRIBUTION AND MYOCARDIAL SUPPLY

In the current era of reperfusion therapy for evolving acute myocardial infarction, it has become popular to refer to the “infarct artery” of the “ventricular myocardium” at risk.

Generally, the basal half of the ventricular septum and the anterior left ventricular free wall is perfused by the LAD coronary artery. A dominant right coronary artery perfuses anterior, lateral and posterior right ventricular myocardium. The posterior coronary artery (most commonly arising from the RCA) supplies blood to the apical half of the ventricular septum and posterior left ventricular free wall. The LCX coronary artery usually perfuses the

lateral wall of the left ventricle (defined as the portion of ventricular myocardium located between anterolateral and posteromedial papillary muscles). Unappreciated areas of coronary perfusion include the basal ventricular septum and left ventricular apex. The basal most portion of the ventricular septum is usually perfused by branches of the PDA. The apical third of the posterior left ventricle may be predominantly perfused by the LAD artery.

At present it is believed that the LAD artery and its branches nourish the apical wall of left ventricle, most of the right and left bundle branches, and the antero lateral papillary muscle of the left ventricle. When the PDA is provided by the circumflex artery, the entire septum is vascularized by the left coronary system⁶³. The LAD artery can also provide collateral circulation to the anterior right ventricle.

CORONARY AUTOREGULATION

Regional coronary blood flow remains constant as coronary artery pressure is reduced below aortic pressure over a wide range when the determinants of myocardial oxygen consumption are kept constant³. This phenomenon is termed autoregulation. Resting coronary blood flow under normal hemodynamic conditions averages 0.7 – 1.0 ml / min / gm and can increase between four and five fold during vasodilation⁴. Circumstances can develop that precipitate subendocardial ischemia in the presence of normal coronary arteries¹.

Coronary flow can be auto regulated to mean coronary pressures as low as 40 mm Hg (diastolic pressures of 30 mmHg³ in humans without ischaemia).

Sub endocardial flow primarily occurs in diastole and begins to decrease below a mean coronary pressure of 40 mmHg³. In contrast, sub epicardial flow occurs throughout the cardiac cycle and is maintained until coronary pressure falls below 25 mmHg. This difference is

primarily related to the increased oxygen consumption in the sub endocardium.

ENDOTHELIUM – DEPENDENT MODULATION OF CORONARY TONE

Furchgott and Zawadzki originally demonstrated that acetyl choline normally dilates arteries via an endothelium – dependent relaxing factors that was later identified to be nitric oxide (NO)⁶. The major endothelium dependent biochemical pathways involved in regulating coronary epicardial and resistance artery diameter are as follows :

1. Nitric Oxide (Endothelium – Derived Relaxing Factor, EDRF)

NO is produced in endothelial cells. Endothelial NO diffuses abluminally into vascular smooth muscle where it binds to guanylate cyclase, increasing cGMP production and causing relaxation through a reduction in intracellular calcium. NO – mediated vasodilation is impaired in many disease states and in patients with one or more risk factors for coronary artery disease (CAD).

2. Prostacyclin

Metabolism of arachidonic acid via cyclooxygenase can also produce prostacyclin, which is a coronary vasodilator when administered exogenously. There is evidence that prostacyclin contributes to tonic coronary vasodilation in humans.

In contrast to the native resistance vasculature, vasodilator prostaglandins are very important determinants of coronary collateral vessel tone and blocking cyclo oxygenase reduces collateral perfusion in dogs.

3. Endothelins

The endothelins (ET-1, ET-2, ET-3) are peptide endothelium – dependent constricting factors. ET is not involved in regulating coronary blood flow in the normal heart but can modulate vascular tone when circulating concentrations increase in pathological states such as heart failure.

METABOLIC MEDIATORS OF CORONARY RESISTANCE

1. Adenosine

It is released from cardiac myocytes and binds to A_2 receptors on vascular smooth muscle, increases cyclic adenosine monophosphate (cAMP), and opens intermediate calcium activated potassium channels⁸. Adenosine has a differential effect on coronary resistance arteries, primarily dilating vessels smaller than $100\mu\text{m}$ ⁷. There is now substantial in vivo experimental data to demonstrate convincingly that it is not required for adjusting coronary flow to increases in metabolism (or) autoregulation⁹. It may, however contribute to vasodilation during hypoxia as well as during acute exercise – induced myocardial ischemia distal to a stenosis⁵.

2. K^+ ATP Channels

Coronary vascular smooth muscle K^+ - ATP channels are tonically active, contributing to coronary vascular tone under resting conditions by causing vasodilation.

3. Hypoxia

Although a potent coronary vasodilatory stimulus, the role of local PO_2 in the regulation of arteriolar tone remains unresolved².

4. Acidosis

Arterial hypercapnea and acidosis (PCO_2) are potent stimuli that have been demonstrated to produce coronary vasodilation² independent of hypoxia.

PARACRINE VASOACTIVE MEDIATORS AND CORONARY VASOSPASM

There are a large number of paracrine factors that can affect coronary tone in normal and pathophysiological states that are unrelated to normal coronary circulatory control.

1. SEROTONIN

Serotonin released from activated platelets causes vasoconstriction in normal and atherosclerotic conduit arteries. Serotonin release generally exacerbates ischemia in CAD.

2. THROMBOXANE A_2

Thromboxane A_2 is a potent vasoconstrictor and can accentuate acute myocardial ischemia.

3. ADENOSINE DIPHOSPHATE (ADP)

ADP is another platelet derived vasodilator that relaxes coronary microvessels as well as conduit arteries.

RISK FACTORS FOR ATHEROTHROMBOTIC DISEASE

Atherothrombosis can no longer be considered a disease of the developed world because by 2025, cardiovascular mortality on a world wide scale will likely surpass that of every major disease group including infection, cancer and trauma^{10,11}.

CONVENTIONAL RISK FACTORS

Smoking

Other than advanced age, smoking is the single most important risk factor for coronary artery disease. Cigarette consumption is the leading preventable cause of death in the United States, where it accounts for more than 4,50,000/- deaths annually¹².

Smokers have been found to have better outcome than non smokers after fibrinolysis in Acute MI in some studies⁷⁴⁻⁷⁸. This was attributed to a more complete reperfusion in smokers after thrombolysis.

In one study⁷⁶, smokers were found to be of relatively younger age, normotensive, male gender and presented with inferior wall infarction more commonly.

Hypertension

High blood pressure often confers silent cardiovascular risk and its prevalence is steadily increasing. In the Framingham Heart Study, even high normal blood pressure (systolic BP → 130 – 139 mmHg, diastolic BP → 85 – 89 mmHg or both) augments risk of cardiovascular disease two fold compared with lower levels¹³.

HYPERLIPIDEMIA AND ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Substantiation of the relationship between total cholesterol and CHD risk emerged from the Multiple Risk Factor Intervention Trial (MRFIT).

HIGH-DENSITY LIPOPROTEIN, CHOLESTEROL, APOLIPOPROTEIN AND OTHER LIPID SUB CLASSES

As is the case with LDL cholesterol, abundant prospective cohort studies have demonstrated a strong inverse relationship between HDL cholesterol and vascular risk. In general, each increase of HDL cholesterol by 1 mg/dl is associated with a 2-3% decrease in risk of total cardio vascular disease. HDL could ferry cholesterol from the vessel wall, augmenting peripheral catabolism of cholesterol¹⁴.

TRIGLYCERIDE – RICH LIPOPROTEINS AND CARDIOVASCULAR RISK

The role of triglycerides remains controversial. Because triglyceride levels tend to vary inversely with HDL cholesterol levels, demonstration of an unequivocal effect of triglycerides on cardiovascular events and mortality independent of HDL levels has proved elusive.

METABOLIC SYNDROME, INSULIN RESISTANCE AND DIABETES

In one major survey, the presence of diabetes conferred an equivalent risk to aging 15 years, an impact greater than that of smoking¹⁵. Insulin resistance alone confers an elevated risk of congestive heart failure and probably explains the association of obesity with this common vascular complication¹⁶.

EXERCISE, WEIGHT LOSS AND OBESITY

Physical exercise reduces myocardial oxygen demand and increases exercise capacity, both of which correlate with lower levels of coronary risk.

Controversy remains as to whether obesity itself is a true risk factor for cardio vascular disease (or) whether its impact on vascular risk is mediated solely through inter relations with glucose intolerance, insulin resistance, hypertension, physical inactivity and dyslipidemia¹⁷.

hs – CRP

Levels of hsCRP greater than 3 mg / lit predict recurrent coronary events, thrombotic complications after angioplasty, poor outcome in the setting of unstable angina, and vascular complications after bypass surgery. Additionally, hsCRP has prognostic usefulness in cases of acute ischemia, even without troponin level elevation, suggesting that an enhanced inflammatory response at the time of hospital admission can determine subsequent plaque rupture¹⁸.

OTHER MARKERS OF INFLAMMATION

These include cytokines such as interleukin – 6, soluble forms of certain cell adhesion molecules such as intercellular adhesion molecule (ICAM-1), p-selectin or the mediator CD40 ligand, as well as markers of leukocyte activation such as myeloperoxidase.

HOMOCYSTEINE

Patients with rare inherited defects of methionine metabolism can develop severe hyperhomocysteinemia (Plasma levels higher than 100 $\mu\text{mol/lit}$) and have markedly elevated risk of premature atherothrombosis as well as venous thromboembolism.

MARKERS OF FIBRINOLYTIC FUNCTION

Impaired fibrinolysis can result from an imbalance between the clot – dissolving enzymes t – PA (or) urokinase type plasminogen activator and their endogenous inhibitors, primarily PAI – 1. Plasma levels of PAI – I peak in the morning. On this basis, a relative hypofibrinolytic state may prevail in the morning. That, along with increased platelet reactivity, may contribute to the increased risk of myocardial infarction seen during this period.

LIPOPROTEIN (a)

Lipoprotein (a) [LP(a)] consists of an LDL particle with its apolipoprotein B – 100 (apo B-100) component linked by a disulfide bridge to apolipoprotein (a) [apo(a)].

More recent studies have suggested that LP(a) binds and inactivates tissue factor pathway inhibitor and may upregulate the expression of plasminogen activator inhibitor further linking lipoproteins and thrombosis.

GENETIC DETERMINANTS OF ATHEROTHROMBOSIS

Some genetic determinants of atherothrombotic cardiovascular disease are well established and have been replicated in multiple cohorts. Carriers of the apoE e4 allele had a 42% higher risk for coronary heart disease compared with those with the more common e3/3 genotype, whereas carriers of the e4 allele, had no significant increase in risk¹⁹. Other potential genetic determinants of myocardial infarction reported in the cardiovascular literature include polymorphisms in the arachidonate 5 – lipoxygenase – activating protein gene and its related pathway,^{20,21} in the cyclooxygenase – 2 gene,²² in the proprotein convertase subtilisin – kexin type 9 (pcsk9)²³ gene, in the 0 x 40 ligand gene²⁴ and in the ROS gene encoding for tyrosine kinase.

ST – ELEVATION MYOCARDIAL INFARCTION PATHOLOGY, PATHOPHYSIOLOGY AND CLINICAL FEATURES

The pathological diagnosis of myocardial infarction requires evidence of myocyte cell death as a consequence of prolonged ischemia. Characteristic findings include coagulation necrosis and contraction band necrosis, often with patchy areas of myocytolysis at the periphery of the infarct.

The clinical diagnosis of MI requires an integrated assessment of the history with some combination of indirect evidence of myocardial necrosis using biochemical, electrocardiographic and imaging modalities.

Of particular concern from a global perspective are projections that the burden of disease in developing countries will become similar to those now afflicting developed countries²⁵.

The short term mortality rate of patients with STEMI who receive aggressive pharmacological reperfusion therapy as part of a randomized trial is in the range of 6.5 – 7.5%²⁸. Where as observational data bases suggest that the mortality rate in STEMI patients in community is 15 – 20%²⁹. In part, this difference relates to the selection of patients without serious Comorbidities for clinical trials.

REVISED DEFINITION OF MYOCARDIAL INFARCTION (MI), CRITERIA FOR ACUTE, EVOLVING (OR) RECENT MI

Either of the following criteria satisfies the diagnosis for acute, evolving (or) recent MI.

1. Typical rise and / or fall of biochemical markers of myocardial necrosis with atleast one of the following :
 - a. Ischemic symptoms
 - b. Development of pathological 'Q' waves in ECG
 - c. ECG changes indicative of ischemia (ST segment elevation (or) depression).
 - d. Imaging evidence of new loss of viable myocardium (or) new regional wall motion abnormality.
2. Pathological findings of an acute MI.

PATHOLOGY

Almost all MIs result from coronary atherosclerosis, generally with superimposed coronary thrombosis. Non – atherogenic forms of coronary artery disease are also there.

Contemporary studies using cardiac magnetic resonance imaging indicate that the development of a Q-wave on the ECG is determined more by the size of the infarct than the depth of mural involvement³⁰. A more suitable framework that puts STEMI in perspective along with unstable angina / non – ST elevation MI (UA / NSTEMI) based on pathophysiology is referred to as the acute coronary syndromes (ACS).

PLAQUE

During the natural evolution of atherosclerotic plaque, especially that which is lipid laden, an abrupt and catastrophic transition can occur, characterized by plaque disruption. Plaque disruption exposes substances that promote platelet activation and aggregation, thrombin generation and ultimately thrombus formation^{31,32}.

The composition of the thrombus may vary at different levels. A white thrombus is composed of platelets, fibrin (or) both and a red thrombus is composed of erythrocytes, fibrin, platelets and leukocytes.

CAUSES OF MYOCARDIAL INFARCTION WITHOUT CORONARY ATHEROSCLEROSIS

1. Arteritis
2. Trauma to coronary arteries
3. Coronary mural thickening with metabolic disease (or) intimal proliferative disease
4. Emboli to coronary arteries
5. Congenital coronary artery anomalies

6. Luminal narrowing by other mechanism
7. Hematological (in situ thrombosis) such as polycythemia vera,
Disseminated Intravascular Coagulation (DIC)
8. Miscellaneous such as cocaine abuse, myocardial contusion.

ACUTE CORONARY SYNDROMES

When plaque disruption occurs, a sufficient quantity of thrombogenic substances is exposed and the coronary artery lumen may become obstructed by a combination of platelets aggregates, fibrin and RBC that may produce an extensive thrombus filling a large segment of the infarct – related artery.

Disruption of plaques is now considered to underlie most acute coronary syndromes (ACS)²⁷. Characteristically, such completely occlusive thrombi lead to a large zone of necrosis typically producing ST elevation on the ECG (STEMI – ST elevation myocardial infarction).

Patients presenting without ST elevation are initially diagnosed as suffering either from unstable angina (or) NSTEMI (Non ST Elevation MI).

Patients presenting with persistent ST segment elevation are candidates for reperfusion therapy (either pharmacological (or) catheter based) to restore flow in the occluded epicardial infarct related artery. ACS patients presenting without ST segment elevation are not candidates for pharmacological reperfusion but should receive anti ischemic therapy, followed by PCI. All patients with ACS should receive antithrombin therapy and antiplatelet therapy regardless of the presence (or) absence of ST – segment elevation.

Prognostic considerations must take into account other important factors, such as whether the ECG abnormality is caused by a first infarct versus subsequent infarct, the location of infarction (anterior versus inferior), infarct size and demographic factors such as patient age²⁶.

CLINICAL FEATURES

Predisposing Factors

Evidence suggests that unusually heavy exercise (particularly in fatigued (or) habitually inactive patients) and emotional stress can precipitate STEMI³³. Such infarction could result from marked increases in myocardial oxygen consumption in the presence of severe coronary arterial narrowing^{35,37}.

CIRCADIAN PERIODICITY

The time of onset of STEMI has a pronounced circadian periodicity, with peak incidence of events between 6 am and noon³⁸.

HISTORY

PRODROMAL SYMPTOMS

The prodrome is usually characterized by chest discomfort, resembling classic angina pectoris, but it occurs at rest (or) with less activity than usual and can therefore be classified as unstable angina.

NATURE OF THE PAIN

The pain of STEMI varies in intensity, in most patients, it is severe and in some instances intolerable. The pain is prolonged, usually lasting for more than 30 mins and frequently for a number of hours. The discomfort is described as constricting, crushing, oppressing (or) compressing. The pain is usually retrosternal in location, spreading frequently to both sides of the anterior chest, with predilection for the left side. In other patients, the discomfort of STEMI radiates to the shoulders, upper extremities, neck, jaw and interscapular region again usually favoring the left side. Both angina pectoris and the pain of STEMI are thought to arise from nerve endings in ischemia (or) injured, but not necrotic myocardium.

The pain often disappears suddenly and completely when blood flow to the infarct territory is restored. In patients in whom reocclusion occurs after fibrinolysis, pain recurs if the initial reperfusion has left viable myocardium. The recognition that pain implies ischemia and not infarction heightens the importance of seeking ways to relieve the ischemia, for which the pain is a marker.

OTHER SYMPTOMS

Nausea and vomiting. Occasionally, a patient complains of diarrhea (or) violent urge to defecate during the acute phase of STEMI. Other symptoms include feelings of profound weakness, dizziness, palpitation, cold perspiration, and a sense of impending doom.

LABORATORY FINDINGS

Serum Markers of Cardiac Damage

Creatine Kinase

Serum CK activity exceeds the normal range within 4 – 8 hrs after the onset of STEMI and declines to normal within 2 – 3 days³⁴.

CREATINE KINASE ISOENZYMES

Although small quantities of CK – MB isoenzyme occur in tissues other than the heart, elevated levels of CK – MB may be considered, for practical purposes, to be the result of MI (except in the case of trauma (or) surgery on the organs containing the enzyme). It has been proposed that a ratio (relative index) of CK – MB mass to CK activity of about 2.5 is indicative of myocardial rather than a skeletal source of the CK – MB elevation.

MYOGLOBIN

The peak levels of serum myoglobin are reached considerably earlier (1 – 4 hrs) than peak values of serum CK. But, it lacks cardiac specificity.

CARDIAC – SPECIFIC TROPONINS

These include troponin C which binds Ca^{2+} , troponin I (TnI) which binds to actin and inhibits actin – myosin interactions, and troponin T (TnT) which binds to tropomyosin, thereby attaching the troponin complex to the thin filament.

Quantitative assays developed for cTnT and cTnI have been approved by the Food and Drug Administration for clinical use³⁹. The troponins cTnT and cTnI begin to rise within 3 hrs

after the onset of STEMI and declines to normal within 7 – 10 days.

CUT – OFF VALUES

CK – MB usually increases ten – twenty folds above the upper limit of the reference range, cTnT and cTnI typically increases more than 20 times above the reference range.

RECOMMENDATIONS FOR MEASUREMENT OF SERUM MARKERS

Retrospective diagnosis (or) diagnosis of MI in the presence of skeletal muscle injury is more readily accomplished with cTnT or cTnI. With increasing familiarity of clinicians with assays for the cardiac – specific troponins, it is anticipated that they will supersede assays for CK – MB not only for the diagnosis of MI but also for assessment of reperfusion, reinfarction, and estimation of infarct size^{40,34}.

ST – ELEVATION MYOCARDIAL INFARCTION : MANAGEMENT

Treatment includes at the time of onset of STEMI (prehospital issues, initial recognition and management in the emergency department, reperfusion), hospital management (medications, arrhythmics, complications, preparation for discharge) and secondary prevention of STEMI.

PREHOSPITAL FIBRINOLYSIS

Several randomized trials have evaluated the potential benefits of prehospital versus in hospital fibrinolysis. There was a generally consistent observation of benefit from earlier treatment and a meta – analysis of all the available trials demonstrated a 17% reduction in mortality⁴². The CAPTIM trial reported a trend toward a lower rate of mortality among STEMI patients receiving pre hospital fibrinolysis as compared with primary PCI, especially if patients were treated with in 2 hrs of the onset of symptoms^{43,44}. The greatest reductions in mortality is observed when reperfusion can be initiated with in 60 – 90 mins of the onset of symptoms⁴¹.

Therefore prehospital fibrinolysis is reasonable in settings in which physicians are present in the ambulance to authorize prehospital fibrinolysis⁴⁵⁻⁴⁷.

GENERAL TREATMENT MEASURES

Apart from Reperfusion Therapy, the following Management Protocol should be followed.

Sample Admitting Orders for the STEMI patient :

1. Condition : serious
2. IV : NS (or) D5W to keep vein open. Start a second IV if IV medication is being given.
3. Vital signs : monitor HR, BP and respiratory rate.
4. Monitor : continuous ECG monitoring for dysrhythmia and ST segment deviation.

5. Diet : NPO except for sips of water until stable.
6. Activity : Bedside commode and light activity when stable.
7. Oxygen : Continuous oximetry monitoring. Nasal cannula at 2 liters / min.
8. Medications :
 - a. Nitroglycerin (NTG)
 - b. Aspirin : (ASA, acetyl salicylic acid)
 - c. Beta - Blocker
 - d. Angiotensin converting enzyme (ACE) inhibitor
 - e. Angiotensin receptor blocker (ARB)
 1. Start ARB orally in patients who are intolerant of ACE inhibitors.
 - f. Pain Medications
 1. IV morphine sulfate 2 -4 mg with increments of 2 – 8 mg IV at 5 – 15 min intervals as needed to control pain.
 - g. Anxiolytics : based on a nursing assessment.
 - h. Daily stool softener.

ASSESSMENT OF REPERFUSION OPTIONS FOR STEMI PATIENTS

Step 1 : Assess time and risk

Step 2 : Determine if fibrinolysis (or) invasive strategy is preferred.

- If presentation is < 3 hrs and there is no delay to an invasive strategy, there is no preference for either strategy.
- Fibrinolysis is generally preferred if :
 - Early presentation (≤ 3 hr from symptom onset and delay to invasive strategy)

An invasive strategy is generally preferred if :

- * Skilled PCI lab is available with surgical back up

Skilled PCI lab is available, defined by
 - Medical contact to balloon (or) door to balloon less than 90 mins.
 - (Door to balloon) – (door to needle) less than 1 hr.
- * High risk from STEMI
 - Cardiogenic shock
 - Killip Class ≥ 3
- * Contraindications to fibrinolysis including increased risk of bleeding and ICH.

- * Late presentation
 - Symptom onset was more than 3 hr ago.
- * Diagnosis of STEMI is in doubt.

(ICH = Intra Cranial Hemorrhage

PCI = Percutaneous coronary intervention

STEMI= ST – Elevation myocardial infarction)

CONTRAINDICATIONS AND CAUTIONS FOR FIBRINOLYTIC USE IN STEMI

Absolute Contraindications

- Any prior intra cranial hemorrhage.
- Known structural cerebral vascular lesion (eg : arterio venous malformations)
- Known malignant intra cranial neoplasm (primary (or) metastatic)
- Ischemic stroke with in 3 months except acute ischemic stroke with in 3 hr.
- Suspected aortic dissection.
- Active bleeding (or) bleeding diathesis (excluding menses).
- Significant closed head (or) facial trauma with in 3 months.

Relative Contraindications

- * History of chronic severe poorly controlled hypertension.
- * Severe uncontrolled hypertension on presentation (SBP > 180 mmHg (or) DBP > 110 mmHg)
- * History of prior ischemic stroke > 3 months, dementia (or) known intra cranial pathology not covered in contraindications.
- * Traumatic (or) prolonged (> 10 min) CPR (or) major surgery (<3wk)
- * Recent (with in 2 – 4 wk) internal bleeding
- * Non compressible vascular punctures
- * For streptokinase / anistreplase : prior exposure (>5 days ago) (or) prior allergic reaction to these agents.
- * Pregnancy
- * Active peptic ulcer

EFFECTS OF MYOCARDIAL REPERFUSION

Rupture of an unstable plaque in the culprit vessel produces complete occlusion of the infarct related coronary artery. STEMI occurs with the ensuing development of left ventricular dilatation and ultimate death through a combination of pump failure and electrical instability. Early reperfusion shortens the duration of coronary occlusion, minimize the degree of ultimate left ventricular dysfunction.

INTRAVENOUS FIBRINOLYSIS

Timi Flow Grade

To provide a level of standardization for comparison of the various regimens, most investigators describe the flow in the infarct vessel according to the thrombolysis in myocardial infarction (TIMI) trial grading system.

Gibson and Co-workers⁵³ developed the TIMI frame count – a simple count of the number of angiographic frames elapsed until the contrast material arrives in the distal bed of the vessel of interest.

Grade 0 : complete occlusion of the infarct related artery,

Grade 1 : some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary bed.

Grade 2 : perfusion of the entire infarct vessel into the distal bed but with delayed flow compared with a normal artery,

Grade 3 : full perfusion of the infarct vessel with normal flow^{49,50}.

The majority of angiographic studies of reperfusion regimens for STEMI used an assessment of the TIMI flow grade at 90 (or) preferably 60 minutes after the start of fibrinolytic therapy⁵¹. TIMI grade 3 flow is far superior to grade 2 in terms of infarct size reduction and both short term and long term mortality benefit⁵². Therefore TIMI grade 3 flow should be considered to be the goal when assessing flow in the epicardial infarct artery⁵².

A convenient, simple, bedside risk scoring system for predicting 30 day mortality at

presentation for fibrinolytic eligible patients with STEMI was developed by Marrow and associates using the time II trial data base^{57,58}.

THE TIMI RISK SCORE FOR ST ELEVATION MYOCARDIAL INFARCTION : A CONVENIENT, BEDSIDE, CLINICAL SCORE FOR RISK ASSESSMENT AT PRESENTATION

- | | | |
|----------------------------------------|---|----------------------|
| 1. Age 65 – 74 / > 75 yrs. | - | 2/3 points |
| 2. Systolic blood pressure < 100 mm Hg | - | 3 points |
| 3. Heart rate > 100 bpm | - | 2 points |
| 4. Killip II – IV | - | 2 points |
| 5. Anterior STE (or) LBBB | - | 1 point |
| 6. Diabetes, h/o HTN (or) | | |
| h/o Angina | - | 1 point |
| 7. Weight < 67 kg | - | 1 point |
| 8. Time of treatment >4 hr | - | 1 point |
| Risk score | - | 0–14 possible points |

(h/o = history of

HTN = hypertension

LBBB = left bundle branch block

STE = ST segment elevation

TIMI = Thrombosis in myocardial infarction)

COMPARISON OF APPROVED FIBRINOLYTIC AGENTS

Dose	Streptokinase	Alteplase	Reteplase	TNK – tpA
	1.5 mu in 30 – 60 min	Upto 100 mg in 90 min (based on weight)	10U x 2 (30 min apart) each over 2 min	30 – 50 mg based on weight
Bolus administration	No	No	Yes	Yes
Antigenic	Yes	No	No	No
Allergic reactions (hypotension most common)	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal
90 – min patency rates (%)	~ 50	~ 75	~ 75	~ 75
TIMI grade 3 flow (%)	32	54	60	63
Cost per dose (U.S. \$)	568	2750	2750	2750 for 50 mg

(TNK = Tenecteplase, TIMI = Thrombolysis in Myocardial infarction)

COMPLICATION OF FIBRINOLYTIC THERAPY

Recent (< 1 yr) exposure to streptococci (or) streptokinase produces some degree of antibody – mediated resistance to streptokinase (and anistreplase) in most patients. Bleeding complications are, of course, most common and potentially the most serious. Most bleeding is relatively minor with all agents. Intra cranial hemorrhage is the most serious complications of fibrinolytic therapy.

There have been reports of, an excess of deaths in the first 24 hrs in fibrinolytic treated patients compared with control subjects (especially in elderly patients treated more than 12 hrs)⁴⁸. However, this excess early mortality is more than offset by the deaths prevented beyond the first day, culminating in an 18% (range 13 – 23%) reductions in mortality by 35 days⁴⁸. The mechanisms responsible for this early hazard are not clear but are probably multiple, including an increased risk of myocardial rupture (particularly in the elderly), fatal intra cranial hemorrhage⁵⁹, inadequate myocardial reperfusion resulting in pump failure and cardiogenic shock⁶⁰ and possible reperfusion injury of reperfused myocardium.

COMPLICATIONS OF MI

HEMODYNAMIC ASSESSMENT :

Hemodynamic Classification of patients with acute myocardial infarction

A.	Based on Clinical Examination	B.	Based on Invasive Monitoring
Class	Definition	Subset	Definition
I	Rales and S ₃ absent	I	Normal hemodynamic PCWP < 18, CI > 2.2
II	Crackles, S ₃ gallop, elevated jugular venous pressure	II	Pulmonary congestion PCWP > 18, CI > 2.2
III	Frank pulmonary edema	III	Peripheral hypoperfusion PCWP < 18 CI < 2.2
IV	Shock	IV	Pulmonary congestion and peripheral hypoperfusion PCWP > 18, CI < 2.2

(A, Modified from Killip T, Kimball J.

B, From Forrester J, Diamond G, Chatterjee K, et al.,)

I. HEMODYNAMIC DISTURBANCES IN MI :

1. Left ventricular failure
2. Cardiogenic shock
3. Free wall rupture causing heart failure
4. Pseudo aneurysm causing heart failure
5. Rupture of the interventricular septum
6. Rupture of a papillary muscle

II. ARRHYTHMIAS :

1. Ventricular premature complexes
2. Ventricular tachycardia
3. Ventricular fibrillation
4. Sinus bradycardia
5. Atrio ventricular block
6. Intra ventricular block
7. Sinus tachycardia
8. Atrial flutter and fibrillation

III. OTHER COMPLICATIONS :

1. Pericardial effusion
2. Pericarditis
3. Dressler syndrome
4. Venous thrombosis and pulmonary embolism
5. Left ventricular aneurysm
6. Left ventricular thrombus and arterial embolism

CORONARY ARTERY BY PASS SURGERY

In 1964, Garrett, Dennis and DeBakey first used CABG as a “bailout” procedure. Widespread use of the technique by Favoloro and Johnson and their respective collaborators followed in the late 1960s. Use of the internal mammary artery (IMA) graft was pioneered by Kolessov in 1967 and by Green and colleagues in 1970.

INDICATIONS FOR CABG

1. Certain anatomical subsets of patients are candidates for CABG, regardless of the severity of symptoms. Such patients include those with:
 - a. Significant left Main CAD;
 - b. Most patients with triple vessel disease that includes the proximal LAD coronary artery, especially those with LV dysfunction (ejection fraction less than 50%)

- c. Patients with chronic stable angina and double vessel CAD with significant proximal disease of the LAD and either LV dysfunction (or) high risk findings on non invasive testing, should also be considered for CABG.
2. The benefits of CABG are well documented in patients with LV dysfunction and multivessel disease, regardless of symptoms.
3. Coronary revascularization with PCI or CABG is highly efficacious in relieving symptoms and may be considered for patients with moderate to severe ischemic symptoms who are not controlled by and / or are dissatisfied with medical therapy even if they are not in a high – risk subset. For such patients, the optimal method of revascularization is selected on the basis of LV function and arteriographic findings and the likelihood of technical success.

COMPARISONS BETWEEN PCI AND CABG

Over a period of 1 – 5 years, the rates of mortality and non fatal infarction were not significantly different between patients revascularized with CABG versus PTCA, but recurrent events, including angina pectoris and the need for repeat revascularization procedures, were significantly more frequent in the PTCA than the CABG group largely as a consequence of incomplete revascularization and restenosis. CABG was found to be associated with higher survival. These reveal the advantages of CABG.

The disadvantages of CABG are cost and morbidity.

OTHER SURGICAL PROCEDURES FOR ISCHEMIC HEART DISEASE

Transmyocardial laser revascularization (TMLR) is performed by placing a laser on the

epicardial surface of the left ventricle. TMLR has been reported to improve symptoms in patients with refractory angina.

MATERIALS AND METHODS

PLACE OF STUDY

This study was conducted in coronary care unit of GRH.

PERIOD OF STUDY

From January 2009 – September 2009

DESIGN

Observational prospective cohort study of patients receiving SK for acute myocardial infarction. A total of 75 patients were included in the study.

METHODOLOGY

SUBJECT SELECTION

1. Inclusion Criteria :

- a. Presence of typical chest pain suggestive of acute myocardial infarction along with ECG evidence of AMI who were thrombolysed.
 - Criteria for thrombolysis being 2 mm (or) more ST elevation in 2 contiguous precordial leads (or) 1 mm (or) more ST elevation in 2 contiguous limb leads.

ECGs were recorded using Hewlett Packard page writer 100 machine.

- b. TW of ≤ 12 hrs from onset of pain to the initiation of thrombolysis.

2. Exclusion Criteria

- a. Late thrombolysis (> 12 hrs from onset of pain)
- b. Recurrent MI
- c. Presence of left bundle branch block
- d. Development of pericarditis
- e. Smokers

DRUG THERAPY

- All patients received SK 1.5 million units in 100 ml NS over 60 minutes.
- Aspirin was given to all patients.
- Use of heparin, β -blockers, ACE inhibitors was according to CCU protocols, which was in accordance with ACC / AHA recommendation.

DEFINITION OF SUCCESS OF THROMBOLYSIS

Success was defined by

1. Clinical – complete subsidence of chest pain.

2. Electrocardiographically – more than 50% ST resolution in a lead which showed maximum ST elevation initially. ST elevation is measured manually, 80 ms after J point from isoelectric line. Preceding PR segment is taken as isoelectric line.

Patients were analysed for success of thrombolytic therapy at 90 mins, after initiation of thrombolytic therapy applying the above mentioned criteria. Those who underwent successful thrombolysis were grouped into a separate category and those who failed thrombolysis were grouped separately.

The following parameters were analysed among them to know whether they influenced the outcome of thrombolysis.

1. Age
2. Sex
3. Systemic hypertension
4. Diabetes mellitus
5. Location of myocardial infarction
6. Time interval between onset of pain and initiation of thrombolytic therapy.

DEFINITION

DIABETES MELLITUS

Patients were considered to be diabetic when :

- 1) currently on oral drugs and / or insulin therapy for DM

(or)

- 2) hyperglycemia detected for the first time at the time of admission and required treatment for it even after discharge.

HYPERTENSION

Patients were considered hypertensive when :

1) they were already on anti – HT medications

(or)

2) medically documented Bp \geq 140/90 mmHg on 2 (or) more occasions after admission and requiring anti hypertensive medications after discharge.

LOCATION OF MI

Inferior Wall infarction

- Patients with ST elevation with (or) without 'q' in L II, III, avf were considered to have inferior wall MI.
- If the similar changes were seen in V₅, V₆, LI, AVL, they were considered to have associated lateral wall MI.
- If they had ST elevation in V_{4R} - V_{6R} (Predominantly V_{4R}), they were considered to have associated RVMI.
- If they had similar changes in V₇ – V₉ associated with mirror image changes in the form of ST depression and a wide R wave (\geq 40 milli secs.) in V₁, V₂, they were considered to have an associated posterior wall MI.

Extensive Anterior Wall Infarction

Patients with ST elevation with (or) without 'q' in $V_1 - V_6$, LI, avL were considered to have extensive AWMI.

ASMI

Patients with ST elevation with (or) without 'q' in $V_1 - V_4$ were considered to have ASMI.

FOLLOW UP

- Patients were followed up until they were discharged from the hospital.
- ECHO was done whenever possible.
- Angiogram was not done due to unavailability.

STATISTICAL METHOD

Bivariate analysis was done by chi- square test and multivariate analysis by logistic regression method.

OBSERVATION AND ANALYSIS

A total of 75 patients were studied and their age ranged from 28 – 72 years (mean 55.26). 62 of them were males (82.7%) and 13 were females (17.3%). 18 of them were hypertensive (24%) and 16 were diabetic (21.3%). 24 patients (32%) had extensive anterior wall infarction, 22 patients (29.3%) had ASMI and 29 patients (38.7%) had inferior wall myocardial infarction. 28 patients (37.3%) were thrombolysed within 0 – 3 hrs from the onset of chest pain, 35 patients (46.7%) were thrombolysed within 3 – 6 hrs from the onset of chest pain and 12 patients (16%) were thrombolysed within 6 – 12 hrs from the onset of chest pain.

Among the patients observed in this study, one patient had died. He had extensive AWMi and had failed thrombolysis.

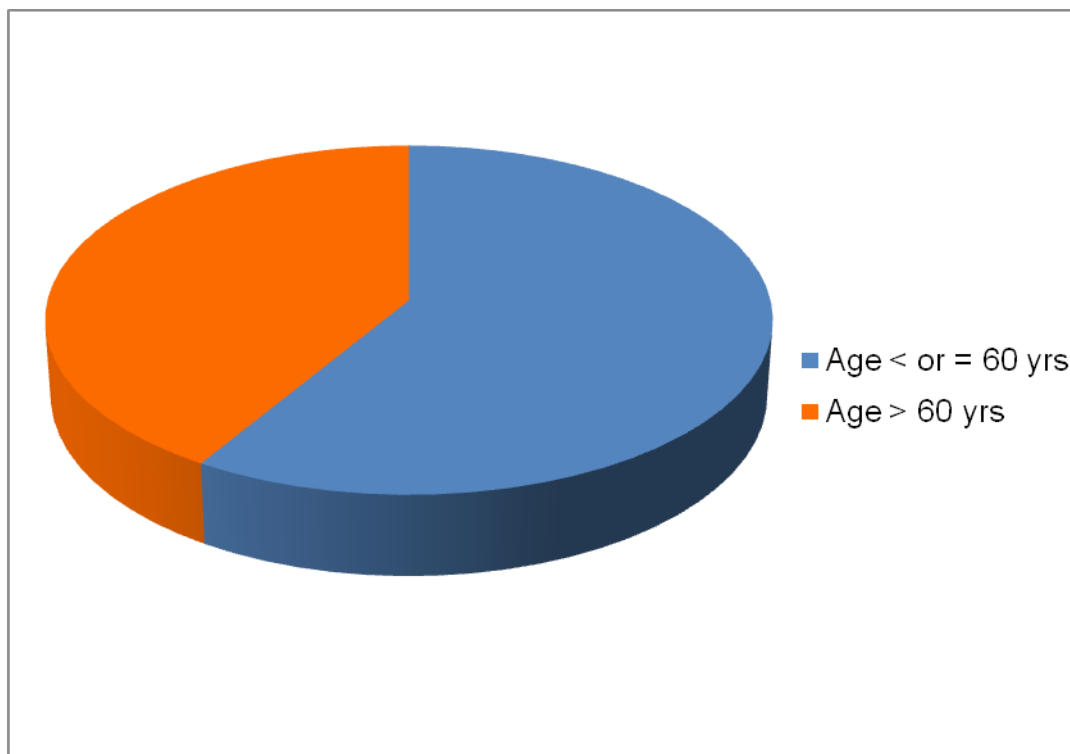
AGE DISTRIBUTION AMONG THE STUDY POPULATION

AGE

	N	Minimum	Maximum	Mean	Std. Deviation
Age	75	28.00	72.00	55.2667	11.76726
Valid N (listwise)	75				

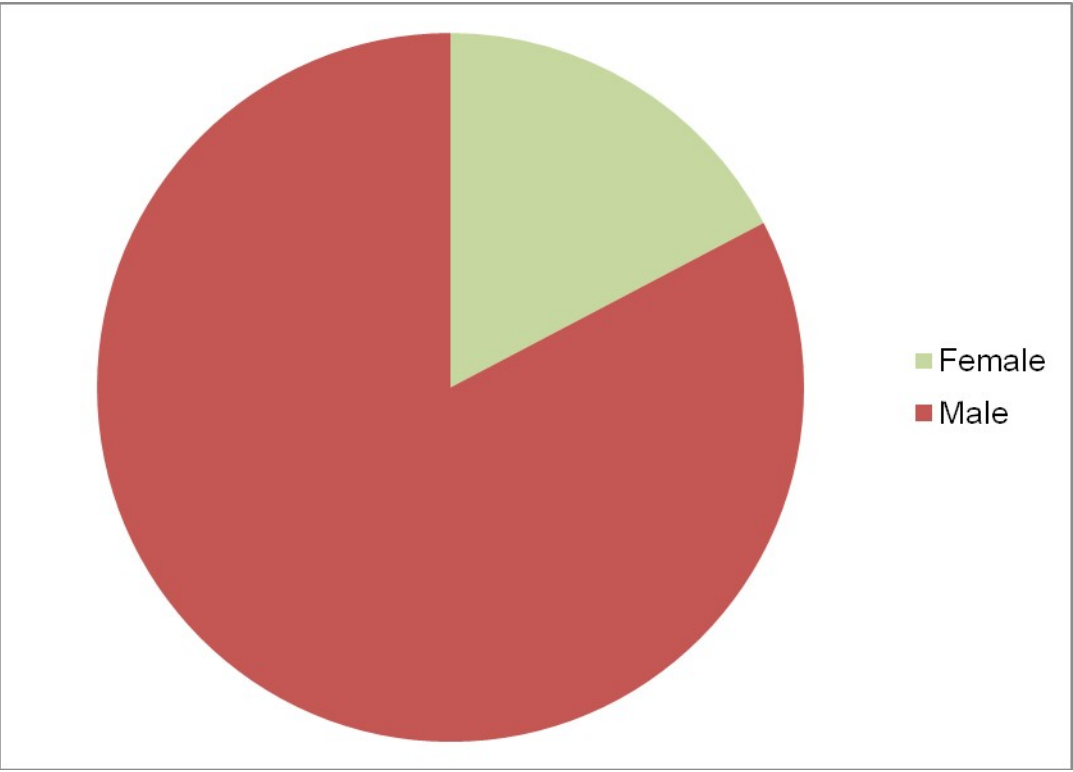
AGE GROUP

Age Group	Frequency	Percent	Valid Percent	Cumulative Percent
< or = 60 yrs	44	58.7	58.7	58.7
> 60 yrs	31	41.3	41.3	100.0
Total	75	100.0	100.0	



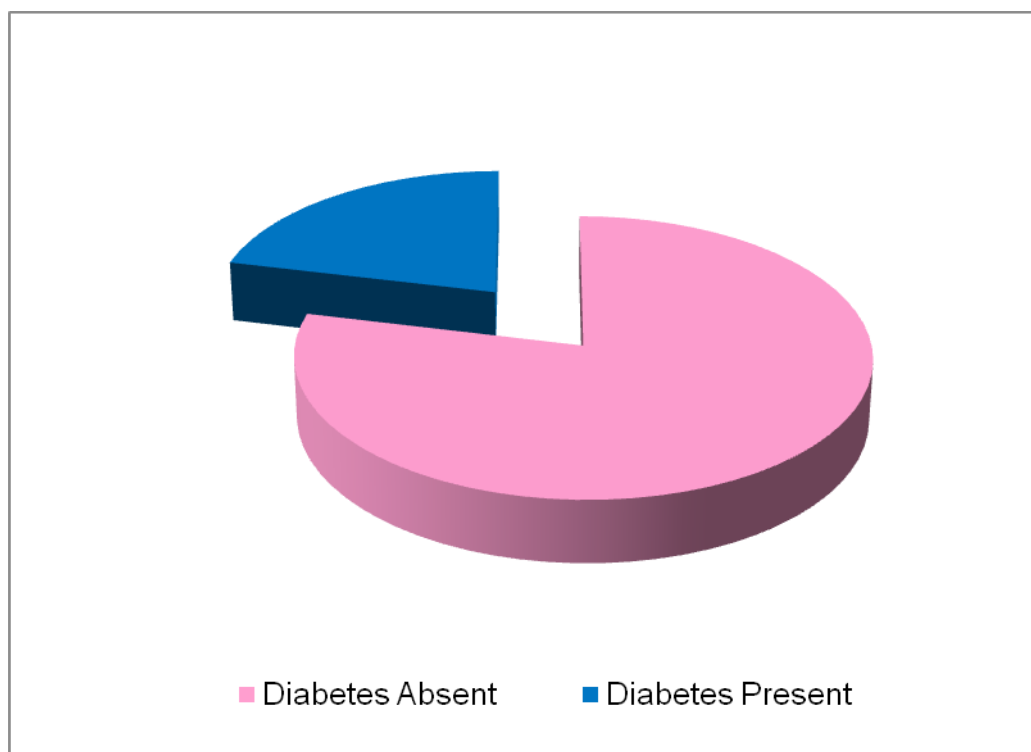
SEX DISTRIBUTION AMONG THE STUDY POPULATION

Sex	Frequency	Percent	Valid Percent	Cumulative Percent
Female	13	17.3	17.3	17.3
Male	62	82.7	82.7	100.0
Total	75	100.0	100.0	



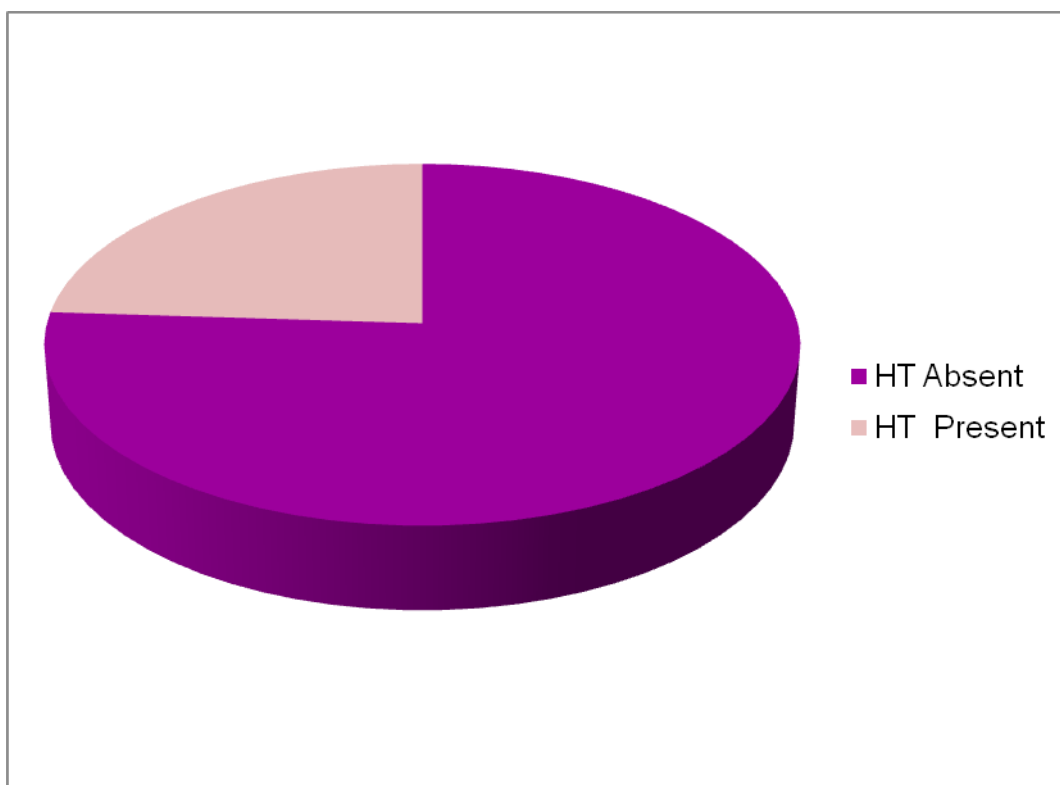
DISTRIBUTION OF DIABETICS AMONG THE STUDY POPULATION

Diabetes Mellitus	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	59	78.7	78.7	78.7
Present	16	21.3	21.3	100.0
Total	75	100.0	100.00	



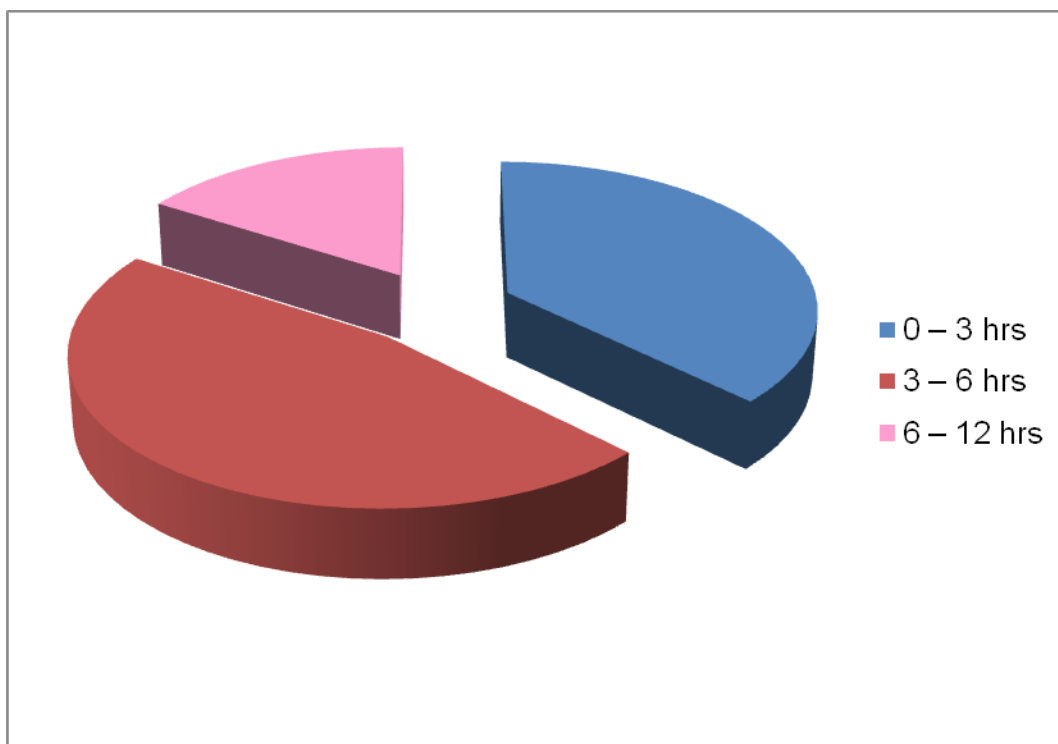
DISTRIBUTION OF HYPERTENSIVES AMONG THE STUDY POPULATION

Systemic Hypertension	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	57	76.0	76.0	76.0
Present	18	24.0	24.0	100.0
Total	75	100.0	100.0	



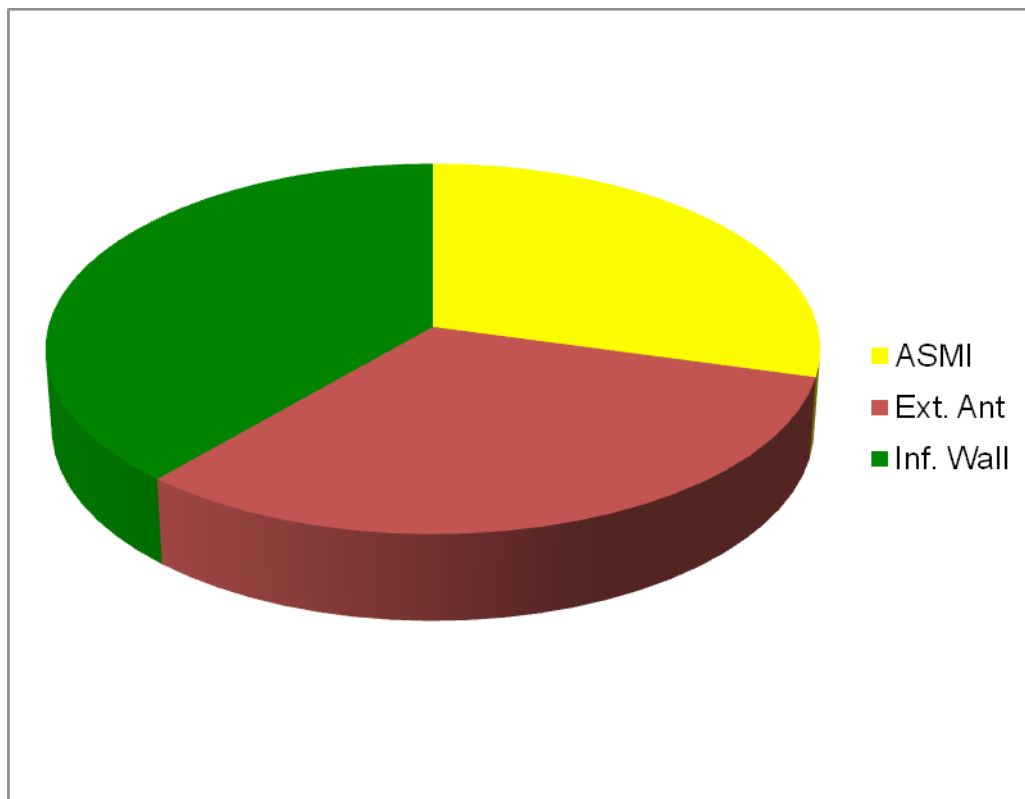
**DISTRIBUTION OF PATIENTS IN DIFFERENT TIME WINDOWS
AMONG THE STUDY POPULATION**

Time Window	Frequency	Percent	Valid Percent	Cumulative Percent
0 – 3 hrs	28	37.3	37.3	37.3
3 – 6 hrs	35	46.7	46.7	84.0
6 – 12 hrs	12	16.0	16.0	100.00
Total	75	100.0	100.0	



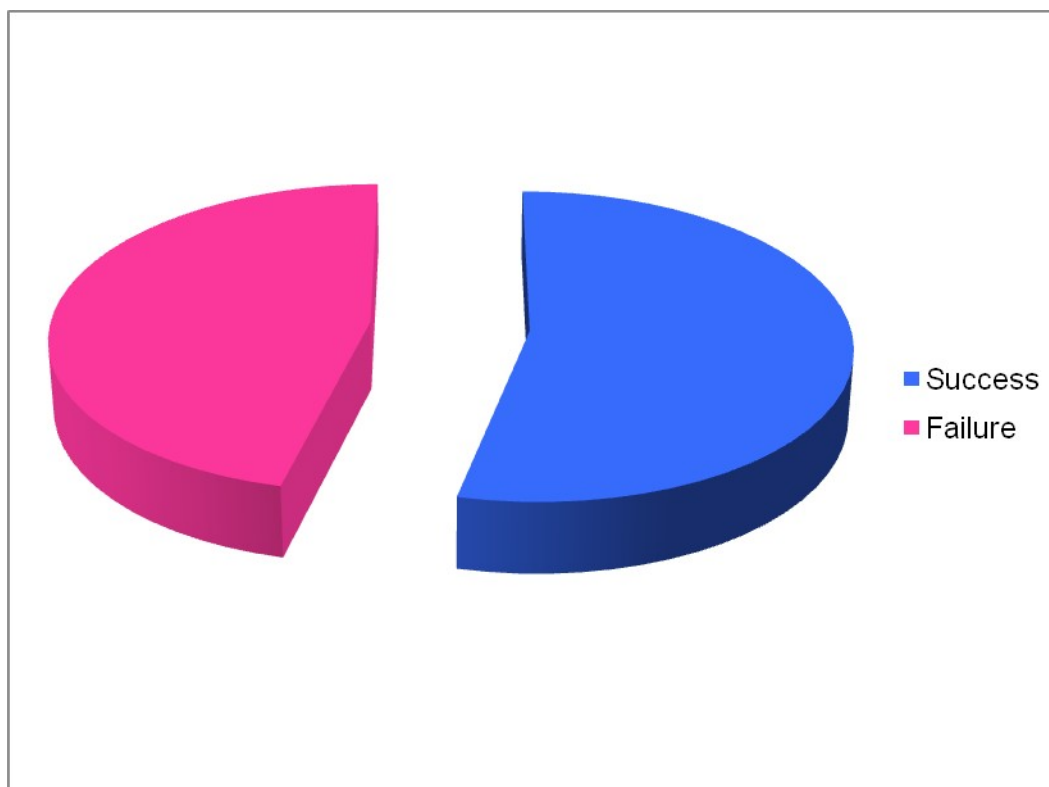
DISTRIBUTION OF PATIENTS WITH DIFFERENT LOCATIONS OF MI AMONG THE STUDY POPULATION

Location of MI	Frequency	Percent	Valid Percent	Cumulative Percent
ASMI	22	29.3	29.3	29.3
Ext. Ant	24	32.0	32.0	61.3
Inf. Wall	29	38.7	38.7	100.00
Total	75	100.0	100.0	



OUTCOME OF THROMBOLYSIS AMONG THE STUDY POPULATION

Outcome	Frequency	Percent	Valid Percent	Cumulative Percent
Success	40	53.3	53.3	53.3
Failure	35	46.0	46.7	100
Total	75	100.0	100.00	100



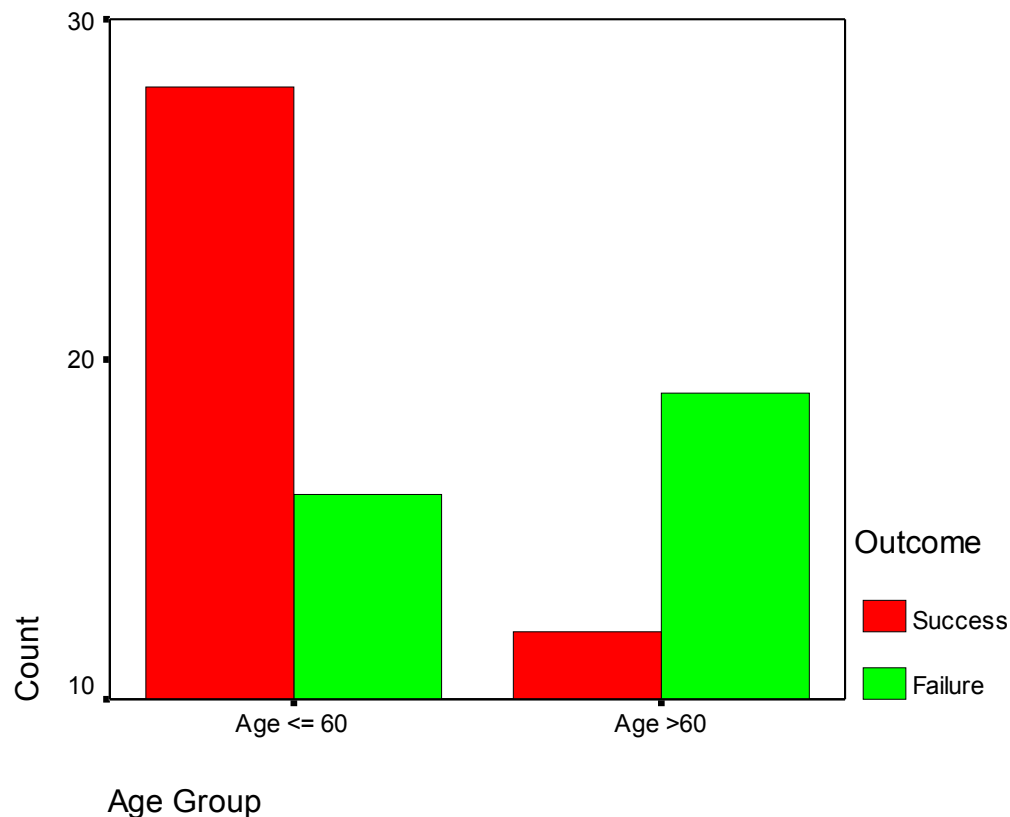
Bivariate Analysis – Study of factors influencing the outcome of thrombolysis in acute myocardial infarction patients

Chi-square test of independence: Comparison of the outcome of thrombolysis between the two age groups

Among the patients with age < 60 years, 28 patients (63.6%) had successful thrombolysis, while 12 patients (38.7%) were successful among those with age > 60 yrs. Age was a significant factor influencing the outcome of thrombolysis in bivariate analysis, but it turned out to be insignificant in multivariate analysis.

Chi-Square Tests

	Value	df	P-value
Pearson Chi-Square	4.540	1	.033



Chi-square test of independence: Comparison of the outcome of thrombolysis between males and females

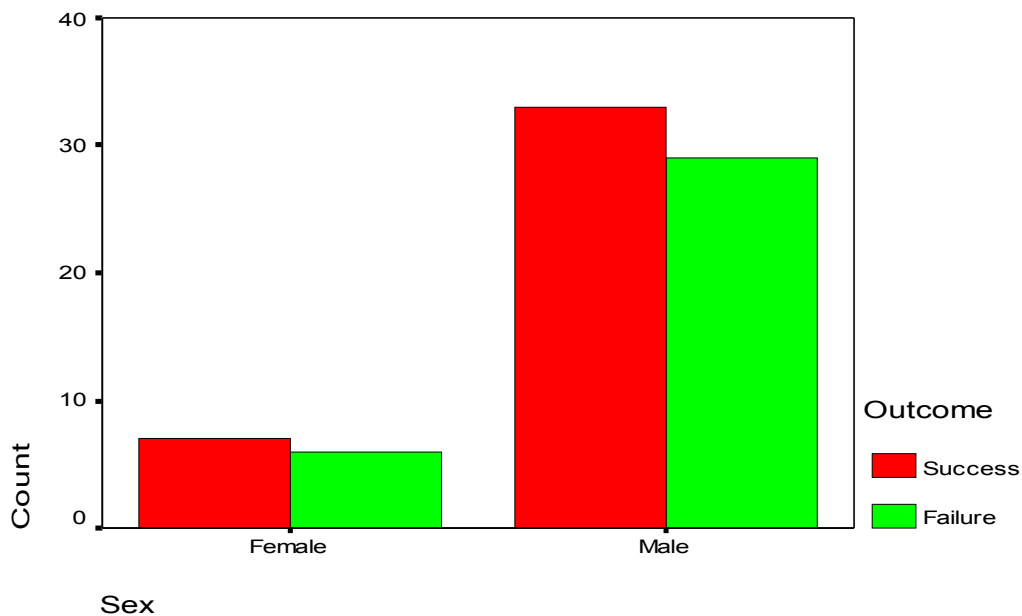
Among the males 33 patients (53.2%) had successful thrombolysis, while among the females 7 patients (53.8%) had successful thrombolysis. The difference was insignificant.

Sex * Outcome Crosstabulation

			Outcome		Total
			Success	Failure	
Sex	Female	Count	7	6	13
		% within Sex	53.8%	46.2%	100.0%
		% within Outcome	17.5%	17.1%	17.3%
	Male	Count	33	29	62
		% within Sex	53.2%	46.8%	100.0%
		% within Outcome	82.5%	82.9%	82.7%
Total	Count		40	35	75
	% within Sex		53.3%	46.7%	100.0%
	% within Outcome		100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	P-value
Pearson Chi-Square	.002	1	.967



Chi-square test of independence: Comparison of the outcome of thrombolysis between diabetics and non-diabetics.

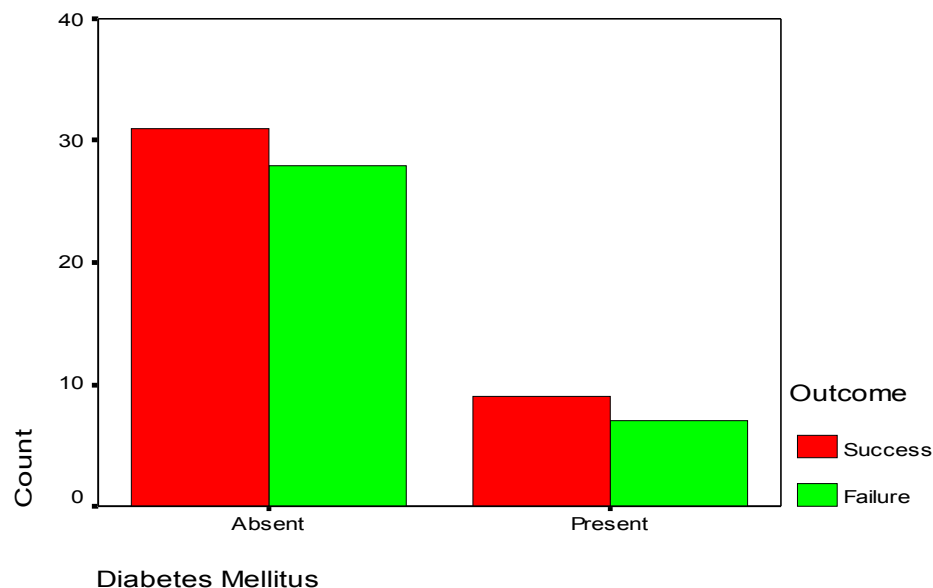
Among the diabetics 9 patients (56.3%) had successful thrombolysis, while among nondiabetics 31 patients (52.5%) had successful thrombolysis. The difference in outcome between diabetics and non diabetics was insignificant.

Diabetes Mellitus * Outcome Crosstabulation

			Outcome		Total
			Success	Failure	
Diabetes Mellitus	Absent	Count	31	28	59
		% within Diabetes Mellitus	52.5%	47.5%	100.0%
		% within Outcome	77.5%	80.0%	78.7%
	Present	Count	9	7	16
		% within Diabetes Mellitus	56.3%	43.8%	100.0%
		% within Outcome	22.5%	20.0%	21.3%
Total	Count	40	35	75	
	% within Diabetes Mellitus	53.3%	46.7%	100.0%	
	% within Outcome	100.0%	100.0%	100.0%	

Chi-Square Tests

	Value	df	P-value
Pearson Chi-Square	.070	1	.792



Chi-square test of independence: Comparison of the outcome of thrombolysis between those with and without hypertension

Among the hypertensives 10 patients (55.6%) had successful outcome while among non

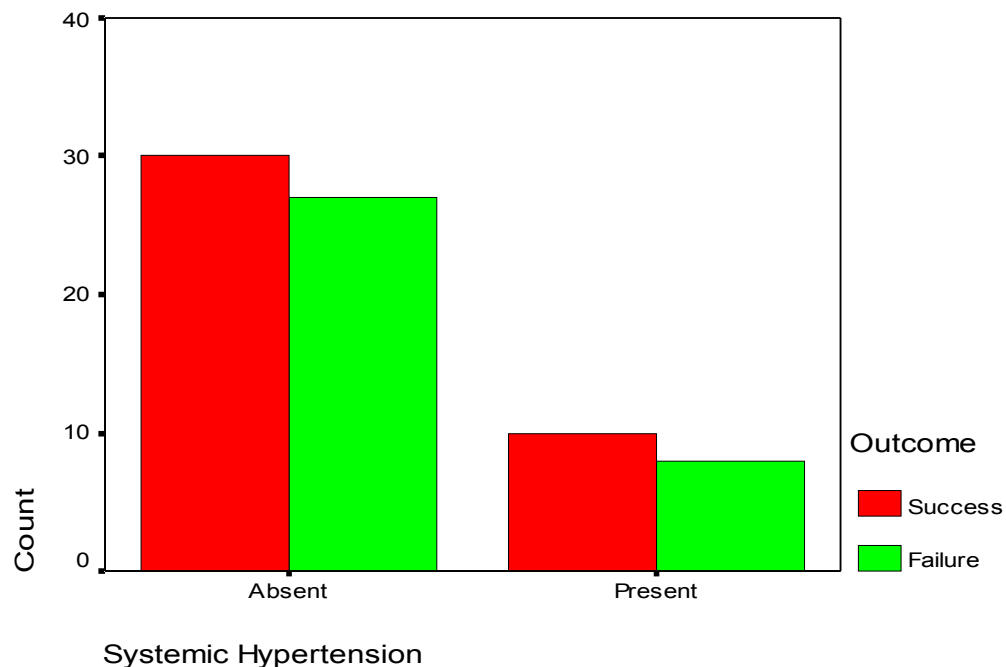
hypertensive 30 patients (52.6%) had successful outcome. The difference in the outcome between the two groups was insignificant.

Systemic Hypertension * Outcome Crosstabulation

			Outcome		Total
			Success	Failure	
Systemic Hypertension	Absent	Count	30	27	57
		% within Systemic Hypertension	52.6%	47.4%	100.0%
		% within Outcome	75.0%	77.1%	76.0%
	Present	Count	10	8	18
		% within Systemic Hypertension	55.6%	44.4%	100.0%
		% within Outcome	25.0%	22.9%	24.0%
Total		Count	40	35	75
		% within Systemic Hypertension	53.3%	46.7%	100.0%
		% within Outcome	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	P-value
Pearson Chi-Square	.047	1	.828



Chi-square test of independence: Comparison of the outcome of thrombolysis between patients presenting in different time windows.

The number of patients who had successful outcome after thrombolysis were 18 (64.3%)

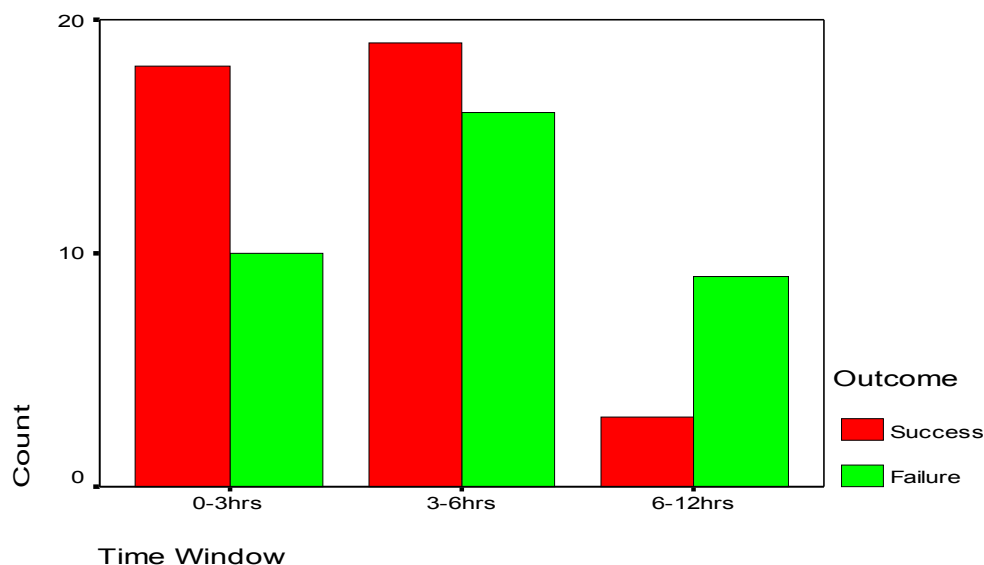
among those in the time window of 0 – 3 hrs, 19 (54.3%) among those in the TW of 3 – 6 hrs and 3 (25%) among those in the TW of 6 – 12 hrs. Patients in 0 – 3 hrs had a higher success rate compared to those in 3 – 6 and 6 – 12 hrs group. The difference between 0 – 3 and 6 – 12 hrs was statistically significant, but the difference between 0 – 3 and 3 – 6 hrs group was statistically insignificant.

Time Window * Outcome Crosstabulation

			Outcome		Total
			Success	Failure	
Time Window	0-3hrs	Count	18	10	28
		% within Time Window	64.3%	35.7%	100.0%
		% within Outcome	45.0%	28.6%	37.3%
	3-6hrs	Count	19	16	35
		% within Time Window	54.3%	45.7%	100.0%
		% within Outcome	47.5%	45.7%	46.7%
	6-12hrs	Count	3	9	12
		% within Time Window	25.0%	75.0%	100.0%
		% within Outcome	7.5%	25.7%	16.0%
Total	Count	40	35	75	
	% within Time Window	53.3%	46.7%	100.0%	
	% within Outcome	100.0%	100.0%	100.0%	

Chi-Square Tests

	Value	df	P-value
Pearson Chi-Square	5.233	2	.073



Chi-square test of independence: Comparison of the outcome of thrombolysis between patients presenting with MI at different sites.

The number of patients who had successful outcome after thrombolysis was 7 (31.8%) among those with ASMI, 11 (45.8%) among those with extensive anterior wall MI and 22

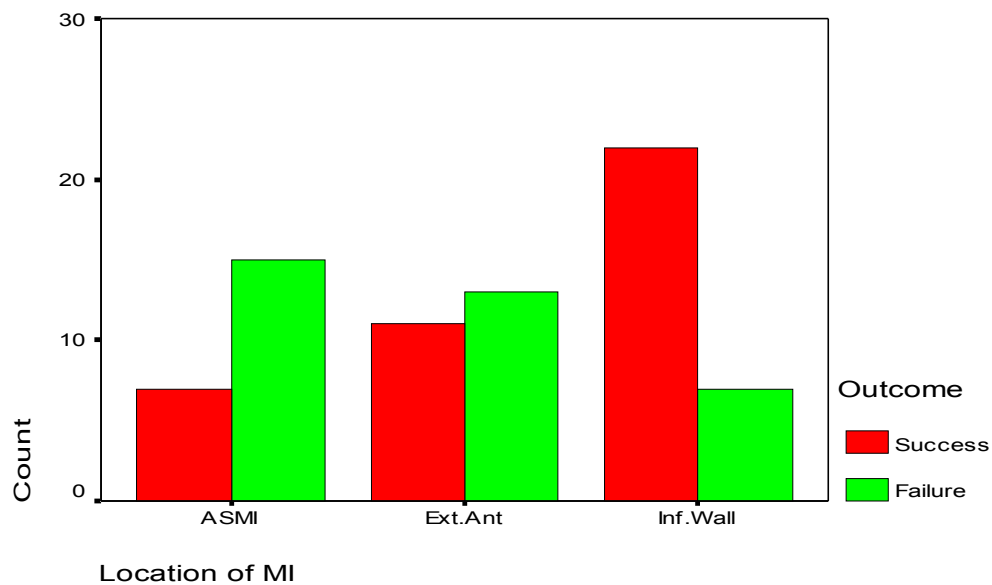
(75.9%) among those with inferior wall MI. Patients with inferior wall MI had higher success rate which was statistically significant.

Location of MI * Outcome Crosstabulation

			Outcome		Total
			Success	Failure	
Location of MI	ASMI	Count	7	15	22
		% within Location of MI	31.8%	68.2%	100.0%
		% within Outcome	17.5%	42.9%	29.3%
	Ext.Ant	Count	11	13	24
		% within Location of MI	45.8%	54.2%	100.0%
		% within Outcome	27.5%	37.1%	32.0%
	Inf.Wall	Count	22	7	29
		% within Location of MI	75.9%	24.1%	100.0%
		% within Outcome	55.0%	20.0%	38.7%
Total	Count	40	35	75	
	% within Location of MI	53.3%	46.7%	100.0%	
	% within Outcome	100.0%	100.0%	100.0%	

Chi-Square Tests

	Value	df	P-value
Pearson Chi-Square	10.548	2	.005



DISCUSSION

INFLUENCE OF AGE OF THE PATIENT ON OUTCOME OF THROMBOLYSIS

Patients > 60 yrs were found to have lesser success rate in bivariate analysis ($p = 0.033$). After adjustment for other parameter in logistic regression, a statistically insignificant difference in success rate is observed but odds ratio 0.947 for age indicates that a year increase in age decreases the odds in favour of success by 6%. This shows that with respect to fibrinolysis elderly people do not behave differently from younger people. This is reflected in decrease of mortality rate among elderly after thrombolysis. In patients aged > 75 years who were treated with SK in GISSI - 2 trials, there were 4.2 fewer deaths per 100 patients than in controls. In ISIS – 2 there was 3.3 fewer deaths per 100 patients in those over 70 yrs of age who were treated. The mortality effect of fibrinolytic therapy in elderly patients is of considerable interest and controversy.

Barriers to initiation of therapy in older patients with STEMI include a protracted period of delay in seeking medical care, a lower incidence of ischemic discomfort and greater incidence of atypical symptoms and concomitant illness and an increased incidence of non – diagnostic ECG readings⁴¹. Younger patients with STEMI achieve a slightly greater relative reduction in mortality compared with elderly patients, but the higher absolute mortality in the elderly results in similar absolute mortality reductions.

Results of FTT group which performed a comprehensive over view of nine trials of thrombolytic treatment, each of which enrolled more than 1000 patients showed, there was a 26% decrease in mortality in patients who were younger than 55 years of age and 4% reduction in mortality in patients older than 75 years of age⁵⁶.

Other studies done to assess the effect of Age on the outcome of thrombolytic therapy

and mortality in Acute MI have shown more beneficial effects in patients less than 55 years^{64,65}.

GENDER

No statistically significant difference was noticed based on gender.

Lunderberg – CF, Topoi et al., performed an angiographic study to find out the patency rate at 90 mins in men versus women. At 90 min TIMI – 3 flow rate was 39% in women and 38% in men, which was not statistically significant.

But 30 day mortality was 13.1% in women versus 8% in men ($p=0.001$).

Thus even though females have a poor outcome after MI, they donot behave differently to thrombolytic treatment.

Some of the studies done to assess the effect of Gender on the outcome of thrombolytic therapy and mortality in Acute MI have shown insignificant differences between male and female sexes⁶⁶⁻⁶⁸.

DIABETES MELLITUS

In this study, success rate of thrombolysis was not found to be different in diabetics from non – diabetic population.

Gray RP, Yudkin J. et al., found a reduction in reperfusion rates in thrombolysed diabetic patients.

Diabetes is a prothrombotic state as reflected by the increased bloodlevels of fibrinogen,

factor VII, vwf. These changes are even more increased if diabetic people happened to be smokers.

Platelet function is also impaired in diabetes. They aggregate more readily to stimuli like ADP and collagen. Glycation of membrane protein due to chronic exposure to high blood glucose levels, change in fluidity of platelet membrane brought about by high concentration of cholesterol and triglycerides are proposed mechanisms for these abnormalities.

On the other hand patients with T₂ DM have profound suppression of fibrinolysis. PA inhibitor I (plasminogen activator) levels are increased in T₂DM, which is responsible for this effect.

Nevertheless thrombolytic therapy should be administered to diabetes with acute MI, because for every 100 patients treated with thrombolytic drugs, four lives are saved.

Results of FTT group which performed a comprehensive overview of nine trials of thrombolytic treatment each of which enrolled more than 1000 patients showed that patients with a history of diabetes mellitus experienced a mortality reduction of 21% compared with a mortality reductions of 15% in patients without diabetes.

Some of the studies done to assess the effect of diabetes on the outcome of thrombolytic therapy and mortality in Acute MI did not show any difference in the outcome between diabetics and non-diabetics⁶⁹⁻⁷¹.

HYPERTENSION

In this study, success rate of thrombolysis is not found to be different in hypertensives from non hypertensives.

Results of FTT group which performed a comprehensive overview of nine trials of thrombolytic treatment each of which enrolled more than 1000 patients showed that there was an 18% decrease in mortality for patients presenting with a systolic pressure less than 100 mmHg, compared with a 12% reduction in mortality for patients with an systolic pressure of 175 mmHg (or) more.

Some of the studies done to assess the effect of hypertension on the outcome of thrombolytic therapy and mortality in acute MI have shown better outcome in non hypertensives than hypertensives^{72,73}.

SITE OF INFARCTION

The major finding of this study is that location of the infarct affects the outcome of thrombolysis. Those with inferior wall MI are 4 times more likely to undergo successful thrombolysis compared to ASMI. (Odds ratio 0.232). This is after adjustment for all confounding variables like time window, age, gender, diabetes and hypertension.

Similar observation were made by Michael Gibson, Sabina, Murphy and E.Brawnwald et al., TIMI study group. They found that TIMI grade III flow rates were lower for left coronary and circumflex artery, compared to RCA after thrombolytic treatment.

The reason for this different response will be evident when we look at the physiology of coronary circulation in right and left coronary artery.

Blood flow in RCA is independent of phases of cardiac cycle, being present in the both systole and diastole, whereas flow in left coronary artery is almost absent during systole and may even be reversed in conditions of heightened microvascular tone and LVH.

The relative thicker wall, the increased wall thickening during systolic contraction and higher intra cavitory pressure of LV may all produce higher intra myocardial pressure than that is observed in the thinner walled right ventricle which is also subjected to lower filling pressure.

More over the extent of necrosis in anterior wall is more resulting in increased myocardial wall edema, compared to inferior wall infarction. This may further decrease the reperfusion rates in anterior wall infarction. Yet another mechanism may be better drug delivery to the RCA and prolonged contact of SK with the thrombus resulting in more efficient fibrinolysis.

TIME WINDOW (TW)

This is the most powerful predictor of success rate which was evident in this study also. The success rate of patients thrombolysed within 3 hrs from onset of symptom was 64.3%. The success rate of patients thrombolysed between 3 and 6 hrs after the onset of symptoms was 54.3%. The success rate of patients thrombolysed between 6 and 12 hrs from the onset of symptoms was 25%.

There is significant difference (sign. at 10%) in the success rate between those thrombolysed in 0 – 3 hours time TW and 6 – 12 hours TW.

Odds ratio of 3.35 indicates that patients in 0 – 3 hours TW group were 3.35 times more likely to have success when compared to patients in 6 – 12 hours TW group.

Early intravenous fibrinolysis undoubtedly improves survival in patients with STEMI⁴¹.

Mortality varies considerably depending on the patients included for study and the adjunctive therapies employed. The benefit of fibrinolytic therapy appears to be greatest when agents are administered as early as possible with the most dramatic results when the drug is given less than 2 hours after symptoms begin⁵⁵.

The data from LATE, EMERAS and the FTT overview form the basis for extending the window of treatment with fibrinolysis upto 12 hrs from the onset of symptoms. Boersma and colleagues pooled the trials in the FTT overview, the two smaller studies with data on time to randomization and the 11 additional trials of more than 100 patients⁵⁵. Patients were divided into six time categories from symptom onset to randomization. A non – linear relationship of treatment benefit to time was observed, with the greatest benefit occurring in the first 1 to 2 hrs from the onset of symptoms⁵⁵.

The impact of time to thrombolytic treatment on outcome in patients with acute MI study by Gibbons and Roberts have shown better outcome with early thrombolysis⁷⁴.

CIRCADIAN VARIATION

Eugene Braunwald et al., noticed a circadian variation in efficacy of thrombolytic treatment with better patency in the evening hours. This is due to circadian variation in the blood levels of PAI – I, which is lower in the evening hours.

In this study no such circadian variation was observed. Probable reasons for this discrepancy may be shorter time window observed in patients presenting in morning hours as well as smaller sample size.

SENSITIVITY AND SPECIFICITY

Sensitivity and specificity of the method used for multivariate analysis here were :

Sensitivity - 75%

Specificity - 68.6%

Mortality differences during days 0 – 35 subdivided by presentation features in collaborative overview of results from nine trials of thrombolytic therapy. The absolute mortality rates are shown for patients who underwent fibrinolysis

Presentation Features	Mortality in Patients after fibrinolytic therapy
ECG	
BBB	18.7%
ST elev, Anterior	13.2%
ST elev, Inferior	7.5%
ST elev other	10.6%
ST depression	15.2%
Other abnormality	5.2%
Normal	3.0%
Hours from onset	
0 – 1	9.5%
2-3	8.2%
4-6	9.7%
7-12	11.1%
13-24	10.0%
Age (years)	
< 55	3.4%
55 – 64	7.2%
65 – 74	13.5%
75+	24.3%
Gender	
Male	8.2%
Female	14.1%
Systolic BP (mm Hg)	
< 100	28.9%
100 – 149	9.6%
150 – 174	7.2%
175+	7.2%
Diabetes	
Yes	13.6%
No	8.7%
All Patients	9.6%

(BBB - bundle branch block, BP - Blood pressure)

From Fibrinolytic Therapy Trialists (FTT) Collaborative Group: Collaborative over view of mortality and major morbidity results from all randomized trials of more than 1000 patients. **Lancet 343:311, 1994.**

SUMMARY

- In this study the overall success rate of thrombolysis among non smokers was 53.3%.
- There was trend towards favourable outcome in those < 60 years and worse outcome in those with age > 60 years. It was statistically insignificant.
- Gender was not found to influence the success rate of thrombolysis.
- Diabetics do not differ from non – diabetics with respect to the success rate of thrombolysis.
- Hypertensive patients did not show any difference from non hypertensive patients with respect to success rate of thrombolysis.
- Time window was a significant factor influencing the outcome in AMI. Patients who presented in the 0–3 hours time window and 3–6 hours time window had higher success rate when compared to patients who presented in time window of 6–12 hrs. Difference in outcome after thrombolysis between 0–3 and 3–6 hrs group was

statistically insignificant.

- Site of infarction was also a significant factor. Patients with Inferior wall MI had significantly higher success rate when compared to ASMI.

CONCLUSION

The study was conducted to evaluate the success rate of thrombolysis in acute MI and the various factors influencing its outcome among non smokers. It was done by observational prospective cohort study of patients receiving SK for acute MI in ICCU in GRH, Chennai.

The overall success rate of thrombolysis among non smokers here was 53.3%.

Patients with inferior wall MI had a significantly better outcome compared to patients with ASMI.

Age influenced the outcome but was not statistically significant.

Early thrombolysis had a better outcome when compared to other factors.

Success rate was 64.3% in those patients thrombolysed within 3 hrs from onset of symptoms. Time window was found to be the most powerful factor influencing the outcome of thrombolysis in patients with acute myocardial infarction.

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ABBREVIATIONS

LAD	-	Left Anterior Descending Artery
LCA	-	Left coronary artery
LCX	-	Left circumflex artery
RCA	-	Right coronary artery
LV	-	Left ventricle
RV	-	Right ventricle
R tpA	-	Recombinant tissue plasminogen activator
CABG	-	Coronary artery bypass Graft
PAI – I	-	Plasminogen activator inhibitor - I
SK	-	Streptokinase
PDGF	-	Platelet Derived growth factor
VWF	-	Von willebrand factor
APSAC	-	Anisoylated plasminogen SK activator complex
LBbB	-	Left bundle branch block
RBbB	-	right bundle branch block
SCD	-	Sudden cardiac death
GRH	-	Government Royapettah Hospital
RVMI	-	Right ventricular myocardial infarction
MI	-	Myocardial infarction
AMI	-	Acute myocardial infarction
DM	-	Diabetes mellitus
SHT	-	Systemic hypertension
ICCU	-	Intensive coronary care unit
GISSI	-	Gruppo Italiano Per lo studio della

- Streptochinasi nell' infarto miocardico.
- GUSTO - Global Utilization of Streptokinase and t-pA for Occluded coronary arteries.
- ISIS - International Study of Infarct Survival.

PROFORMA

Name : IP :
 Age : Occupation :
 Sex : Monthly income :

Personal Data :

1. Smoking Yes No
 If Yes – No. of Cigarettes / day

2. Drinking Yes No
 If Yes – ml / week

3. Life Style

Exercise regularly ≥ 3 times / week	Active
	Sedentary

4. Hypertension Yes No
 If yes, 1) Duration
 2) Treatment regular / irregular

5. Diabetes Yes No

If Yes,

Duration -	
Type I	Type II

Insulin	
Oral Durgs	

6. Hyper lipidemia Yes No

Treatment with

- a. Diet alone
- b. Drugs

- a. Hyper triglyceremia
- b. Hyper cholesterolemia
- c. Mixed
- d. Other diseases – specify

Family history of

SCD	AMI	Stroke
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Time of onset of symptoms

0 – 6 AM	6 – 12 noon	12 – 6 pm	6 – 12 midnight

Physical Examination

Pulse -
 Bp -
 JVP -
 S3 -
 Crackles -
 Murmur -
 Rub -

Time of SK administration

0 – 6 AM	6 – 12 noon	12 – 6 pm	6 – 12 midnight

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Pain onset to SK administration interval in hrs.

0 – 3 hrs	3 – 6 hrs	6 – 12 hrs

ECG on admission

1. Location of MI

Ext. Ant	AS	AL	Inf.	IP	IPL	RVMI

2. Peak ST elevation in millimeter

ECG at 90 min after SK therapy :

Maximal ST elevation in mm

Percentage ST resolution

Clinical condition at 90 mins

- No angina
- Decreased pain
- Persistent with same intensity

Arrhythmias if any during thrombolysis -

Thrombolysis successful

Other events and intervention if any

Lab data :

Hb%, TC, DC, ESR
Sugar
Urea
Creatinine

Na⁺,
K⁺

Echo

Angiogram

Follow up